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Therapeutic Class Review
Cholesterol Absorption Inhibitors

I. Overview

At the time of this review, ezetimibe is the only antilipemic agent that is classified as a cholesterol absorption inhibitor via the American Hospital Formulary Service (AHFS).[1-2] Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing compounds. Ezetimibe reduces blood cholesterol by inhibiting the absorption of both dietary and biliary cholesterol by the small intestine resulting in a decrease in hepatic cholesterol stores, an increase in hepatic cholesterol sequestering from the circulation, and ultimately to lower systemic cholesterol levels.[1,3]

Table 1 lists all the cholesterol absorption inhibitors included in this review. This review encompasses all dosage forms and strengths.

Table 1. Cholesterol Absorption Inhibitors Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)
ezetimibe	tablet	Zetia®

No generic products are available in this class.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the cholesterol absorption inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Cholesterol Absorption Inhibitors

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)[4]**	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low-density lipoprotein cholesterol (LDL-C)-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial

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Clinical Guideline	Recommendation
	hypercholesterolemia. Polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report (2002)**[5]	General Recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Cholesterol Absorption Inhibitors • Cholesterol absorption inhibitors (eg, ezetimibe) are not mentioned in this guideline.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[6]	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–high-density lipoprotein cholesterol (HDL-C) include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy).
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[7]	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)**[8]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be

Clinical Guideline	Recommendation
	considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[9]	• Statins are considered first-line drugs for lowering LDL-C. • As monotherapy, cholesterol absorption inhibitors have mild LDL-lowering effects and can be used for patients with active liver disease, having adverse effects on statins or when statins, fibrates and nicotinic acid are contraindicated. • Their primary role in therapy is in combination with statins. • Cholesterol absorption inhibitors have not been shown in clinical trials to reduce myocardial infarction and coronary death. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

III. Indications

Food and Drug Administration (FDA)-approved indications for the cholesterol absorption inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Cholesterol Absorption Inhibitors[3]

Indication(s)*	Ezetimibe
When administered alone, as adjunctive therapy to diet for the reduction of elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (apo B) in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia	✔
When administered in combination with a hydroxyl-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, and apo B in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia	✔
When administered in combination with fenofibrate, as adjunctive therapy to diet for the reduction of elevated TC, LDL-C, apo B, and non-high-density lipoprotein cholesterol (non–HDL-C) in patients with mixed hyperlipidemia	✔
When administered in combination with atorvastatin or simvastatin, for the reduction of elevated TC and LDL-C levels in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (eg, low-density lipoprotein apheresis) or if such treatments are unavailable	✔
When administered alone, as adjunctive therapy to diet for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia	✔

*Prior to initiating therapy with ezetimibe, secondary causes for dyslipidemia (ie, diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL-C and decrease HDL-C) should be excluded or, if appropriate treated.[3]

IV. Pharmacokinetics

The pharmacokinetic parameters for the cholesterol absorption inhibitors are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Cholesterol Absorption Inhibitors[3,10]

Drug	Bioavailability (%)	Protein Binding (%)	Metabolism	Active Metabolites	Elimination (%)	Half-Life (hours)
Ezetimibe	35-60	>90	Glucuronide conjugation with minimal oxidation	ezetimibe-glucuronide	Feces: 78 Urine: 11	22 for both drug and active metabolite

V. Drug Interactions

Significant drug interactions with the cholesterol absorption inhibitors are listed in Table 5.

Table 5. Significant Drug-Drug Interactions with Cholesterol Absorption Inhibitors[3,10,11]

Drug	Significance Level	Interaction	Mechanism
Ezetimibe	2	Cyclosporine	Although the mechanism is unknown, when cyclosporine and ezetimibe are administered concomitantly exposure to both drugs may be increased, potentially increasing the pharmacologic effects and adverse reactions. Monitor cyclosporine concentrations when ezetimibe is coadministered and adjust the cyclosporine dose as needed. In addition, monitor patients for cyclosporine or ezetimibe adverse reactions.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

Common side effects of ezetimibe include abdominal pain, diarrhea, arthralgia, back pain, myalgia, headache, cough, sinusitis and fatigue. More serious side effects include hepatitis, drug-induced myopathy and rhabdomyolysis. The most common adverse drug events reported with the cholesterol absorption inhibitors are noted in Table 6.

Table 6. Adverse Drug Events (%) Reported with Cholesterol Absorption Inhibitors[3,10]

Adverse Event	Ezetimibe
Cardiovascular	
Chest pain	1.8-3.4
Central Nervous System	
Depression	✔
Dizziness	1.8-2.7
Fatigue	1.9-2.8
Headache	6.3-8
Dermatologic	
Rash	✔
Urticaria	✔
Endocrine and Metabolic	
Cholecystitis	✔
Cholelithiasis	✔
Elevated creatine phosphokinase	✔
Elevations in liver transaminase	2.7
Hepatitis	✔
Pancreatitis	✔
Gastrointestinal	
Abdominal pain	2.7-3.5
Diarrhea	2.8-3.7
Nausea	✔
Hematologic	
Thrombocytopenia	✔
Musculoskeletal	
Arthralgia	3.4-3.8
Back pain	3.4-4.3
Myalgia	4.5-5.0
Myopathy	Very rarely

Adverse Event	Ezetimibe
Rhabdomyolysis	Very rarely
Respiratory	
Angioedema	✔
Coughing	2.3
Pharyngitis	2.3-3.1
Sinusitis	3.5-4.6
Upper respiratory tract infection	11.8-13
Other	
Anaphylaxis	✔
Cholecystectomy	1.7
Hypersensitivity reactions	✔
Infection viral	2.2

✔ Percent not specified

VII. Dosing and Administration

No dosage adjustment of ezetimibe is necessary in patients with mild hepatic insufficiency or renal insufficiency. There is limited experience with ezetimibe in the pediatric population and it is not recommended to be used in children less than 10 years of age. The usual dosing regimens for the cholesterol absorption inhibitors are summarized in Table 7.

Table 7. Usual Dosing for the Cholesterol Absorption Inhibitors[3,10]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Ezetimibe	10 mg once daily	Safety and efficacy in children (<10 years of age) have not been established.	Tablet: 10 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cholesterol absorption inhibitors are found in Table 8.

Table 8. Comparative Clinical Trials Using Cholesterol Absorption Inhibitors

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dujovne et al[12] Ezetimibe 10 mg QD vs placebo	DB, MC, PC, RCT Adult men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout)	N=892 12 weeks	Primary: Percent change from baseline to end point in plasma concentration of direct LDL-C Secondary: Changes and percent changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, and HDL-C at end point, changes from baseline HDL_2-C and HDL_3-C, apo AI, apo B, Lp(a) at end point, adverse events	Primary: The ezetimibe group achieved a mean percent reduction from baseline to end point in the plasma concentration of LDL-C of 16.9% compared to 0.4% in the placebo group (P<0.01). Secondary: There was a –17.68% compared to a 1.11% change in the calculated LDL-C from baseline in the ezetimibe and placebo groups, respectively (P<0.01). Ezetimibe also significantly decreased the apo B, TC, and TG as well as significantly increased HDL-C and HDL_3-C from baseline (P<0.01). However, there was no significant change in HDL_2-C and apo AI with ezetimibe compared to placebo (P=0.76 and P=0.50, respectively). Treatment-emergent adverse events occurred in 66% of patients taking ezetimibe and 63% of patients taking placebo. The most commonly reported adverse event in both treatment groups were upper respiratory tract infections and headache. The adverse events were considered to be mild to moderate and were similar between treatment groups (P value not reported).
Knopp, Gitter et al[13] Ezetimibe 10 mg QD vs	DB, MC, PC, RCT Adult men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia	N=827 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of	Primary: The mean plasma concentration of direct LDL-C from baseline to end point was 17.7% in the ezetimibe group compared to 0.8% in the placebo group (P<0.01). Secondary: Ezetimibe significantly decreased calculated LDL-C, apo B, TC and Lp(a) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo	(calculated LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL)		direct LDL-C Secondary: Changes and percentage changes from baseline in LDL-C (calculated via the Friedewald equation), TC, TG, HDL-C at end point, HDL_2-C, HDL_3-C, apo AI, apo B, Lp(a), adverse events	significantly increased HDL-C and HDL_2-C ($P\leq0.01$ for all). However, the change in HDL_3-C, apo AI, and TG from baseline did not result in significant differences between treatment groups (P=0.49, P=0.27, P=0.09). The percentage of patients reporting treatment-emergent adverse events was 61% in the ezetimibe group and 65% in the placebo group. No individual adverse event was prevalent in either group and all were considered mild to moderate in severity. Overall, the adverse event profiles were similar between both treatment groups (P value not reported).
Knopp, Dujovne et al[14] Ezetimibe 10 mg QD vs placebo	DB, MC, PC, RCT Pooled data of men and women aged ≥18 years with a diagnosis of primary hypercholesterolemia (calculated LDL-C 130 to 250 mg/dL and plasma TG ≤350 mg/dL after adequate lipid-lowering drug washout) Includes the 827 patients from Knopp, Gitter, et al (above) plus 892 patients from a second study.	N=1,719 (2 trials) 12 weeks	Primary: Percentage change from baseline to end point in the plasma concentration of LDL-C Secondary: Percentage change from baseline in TC, TG, HDL-C, HDL_2-C, HDL_3-C, apo AI, apo B, Lp(a), adverse events	Primary: In the pooled analysis, LDL-C was reduced by a mean 18.2% from baseline in the ezetimibe group compared to an increase of 0.9% in the placebo group (P<0.01). Secondary: Ezetimibe significantly decreased TC, apo B, Lp(a), and TG and increased HDL-C compared to placebo (P<0.01). However, there were no statistically significant differences in the change of HDL_2-C, HDL_3-C and apo AI between ezetimibe and placebo (P=0.08, P=0.06, and P=0.26). The overall adverse event profiles were similar between the ezetimibe and placebo groups. Approximately 62% of patients in the ezetimibe group and 62% of patients in the placebo group reported adverse events. Also, there were no significant between-group differences in the laboratory or clinical safety parameters or gastrointestinal, liver, or muscle side effects.
Wierzbicki et al[15]	PRO	N=200	Primary: LDL-C, TG, HDL-	Primary: Ezetimibe was associated with 7% reductions in LDL-C and 11% reductions in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD vs placebo QD	Patients with refractory familial hyperlipidemia or intolerance to statin therapy	Not reported	C, CRP, ALT Secondary: Not reported	apo B. The proportion of patients achieving LDL-C <3 mmol/L increased from 6% to 18%. There were no significant differences in TG, HDL-C, CRP, or ALT. Secondary: Not reported
Kalogirou et al[16] Ezetimibe 10 mg QD vs placebo	PRO Patients with primary dyslipidemia and no evidence of CHD, average 54 years of age, average BMI of 26.9 kg/m^2	N=50 16 weeks	Primary: Effect of monotherapy ezetimibe on lipoprotein subfractions Secondary: Not reported	Primary: A significant median reduction in serum HDL-C concentration from 1.5 mmol/L (1.1 to 2.6) at baseline to 1.4 mmol/L (0.9 to 2.6) posttreatment was observed with ezetimibe treatment. The median change in HDL-C was –6.6% (*P*<0.001). A significant median reduction in TC from 7.1 mmol/L (4.9 to 11.1) at baseline to 5.8 mmol/L (4.3 to 8.9) posttreatment was observed with ezetimibe treatment. The median change in TC was –15.5% (–34.5% to 4.2%) with ezetimibe treatment (*P*<0.001 vs placebo). Mean serum TG decreased from 1.5 mmol/L (0.6 to 4.28) at baseline to 1.4 mmol/L (0.6 to 3.2) posttreatment; a median percent change of 9.3% (–32.4% to 15.7%; *P*<0.05). Mean serum LDL-C levels significantly decreased from 3.8 mmol/L (2.5 to 7.3) at baseline to 3.2 mmol/L (1.8 to 5.4) posttreatment; a median percent change of –20.1% (–51.1% to 23.1%; *P*<0.001). Secondary: Not reported
Gonzalez-Ortiz et al[17] Ezetimibe 10 mg QD vs placebo QD	DB, PC, RCT Obese, dyslipidemic patients 18-45 years old	N=12 90 days	Primary: TC, LDL-C Secondary: HDL-C, TG, VLDL	Primary: Ezetimibe-treated patients compared with placebo-treated patients had decreased TC (6.0 vs 4.2 mmol/L; *P*=0.011) and LDL-C (4.0 vs 2.2 mmol/L; *P*=0.003) without affecting insulin sensitivity. Secondary: There were no differences in HDL-C, TG, and VLDL (*P*=not significant).
Gagné, Bays et al[18]	DB, MC, PC, RCT	N=769	Primary: Mean percentage	Primary: There was an additional LDL-C reduction of 25.1% in patients receiving

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD plus a statin vs placebo plus a statin	Adults aged ≥18 years, currently on a stable daily dose of a statin for ≥6 weeks, must have been previously instructed on a cholesterol-lowering diet, LDL-C at or above recommended target level for patient's risk category (<160 mg/dL for patients without CHD and ≤1 risk factor, <130 mg/dL for patients without CHD and ≥2 risk factors, ≤100 mg/dL for patients with established but stable CHD or CHD-equivalent disease)	8 weeks	change in LDL-C from baseline to end point Secondary: Percentage of patients who achieved NCEP ATP II target levels for LDL-C, HDL-C, TC, TG, adverse events	ezetimibe therapy compared to a reduction of 3.7% in patients receiving placebo (*P*<0.001 for between-group differences). Secondary: Including patients who were technically at LDL-C goal at baseline, 75.5% of patients taking ezetimibe plus statin achieved the prespecified NCEP ATP II target LDL-C levels at end point compared to 27.3% of patients taking placebo plus statin (OR, 19.6; *P*<0.001). For those patients who were not at target LDL-C levels at baseline, 71.5% vs 18.9% of patients taking ezetimibe and placebo, respectively, achieved target LDL-C goals. HDL-C was increased by 2.7% compared with an increase of 1.0% in patients taking ezetimibe and placebo, respectively (*P*<0.05). TG decreased by 14.0% and 2.9%, respectively (*P*<0.001). TC was also improved significantly with coadministration of ezetimibe compared to placebo (*P*<0.001). The overall incidence of treatment-related adverse events was similar between both groups (21% ezetimibe vs 17% placebo; *P* value not reported).
Pearson, Francis et al[19] Ezetimibe 10 mg QD Patients either received ezetimibe as monotherapy, in combination with a low-dose statin (20 mg/day or less of atorvastatin or its	RETRO Cohort Men and women ≥18 years old who took ezetimibe for a minimum of two weeks	N=84 2-6 weeks	Primary: Change in fasting lipid profile at baseline to 2-6 weeks of ezetimibe therapy, clinical effectiveness results stratified by primary versus secondary prevention Secondary:	Primary: The mean reductions from baseline to 2-6 weeks of ezetimibe therapy were: TC 1.11mmol/L (16.5%), LDL-C level 1.01 mmol/L (22.3%), and ratio of TC:HDL 0.68 mmol/L (12.8%) (all *P*<0.001). The HDL-C level increased by 0.06 mmol/L (4.6%) from baseline to 2-6 weeks of ezetimibe therapy (*P*<0.001). Results were similar when stratified by primary (N=28) versus secondary (N=56) prevention. Among the primary prevention group, only the TC levels, LDL-C levels and TC:HDL ratio reductions were statistically significant (*P*<0.001). In the secondary prevention group, the reductions in TC levels, LDL-C levels, HDL-C levels and TC:HDL ratio all achieved statistical significance (*P*<0.001). LDL-C level reductions from baseline, stratified by drug regimen, were –1.03

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
equivalent), or in combination with a high-dose statin (20 mg/day or more of atorvastatin or its equivalent).			Percentage of patients able to achieve their LDL-C target levels in accordance with their calculated Framingham risk category and defined Canadian guidelines and safety and tolerability	mmol/L (–20.5%) for ezetimibe monotherapy, –1.19 mmol/L (–30.1%) for ezetimibe and a low-dose statin, and –0.95 mmol/L (–22.5%) for ezetimibe plus a high-dose statin (*P*<0.001 for ezetimibe monotherapy and ezetimibe plus a high-dose statin; *P*=0.0017 for ezetimibe plus a low-dose statin). Secondary: There were 7 patients out of 34 (20.6%) in the ezetimibe monotherapy group, 5 out of 12 (41.6%) in the ezetimibe plus low-dose statin group and 18 out of 38 (47.4%) in the ezetimibe plus high-dose statin group who achieved previously unattainable target LDL-C levels. There were 4 patients who discontinued therapy due to treatment-related adverse event.
Bissonnette et al[20] Ezetimibe 10 mg QD coadministered with current statin therapy	MC, OL, PRO Men and women ≥18 years of age with a confirmed diagnoses of hypercholesterolemia and elevated plasma LDL-C levels of ≥2.5 mmol/L for patients at high 10-year CAD risk, ≥3.5 mmol/L for patients at moderate 10-year CAD risk and ≥4.5 mmol/L for patients at low 10-year CAD risk category, on a stable diet and statin regimen for at least 4 weeks before study entry	N=953 6 weeks	Primary: Percentage of change in LDL-C during the 6-week treatment period Secondary: Percentage of patients who had achieved the recommended target LDL-C levels at the end of the 6-week treatment period and the percentage of change in TC, TG, HDL-C , apo B and the TC:HDL-C ratio and safety and tolerability	Primary: After 6 weeks of treatment with ezetimibe, a statistically significant mean reduction was observed in LDL-C (30.5%; *P*<0.001). Secondary: At 6 weeks, 674 patients (80.5%) achieved the recommended target LDL-C levels. After 6 weeks of treatment with ezetimibe, statistically significant mean reductions were observed in TC (20.8%), TG (10.1%), apo B (19.8%), and TC:HDL ratio (19.9%) (*P*<0.001). There were 50 mild, nonserious adverse events related to ezetimibe reported by 32 patients (3.4%). Frequently reported adverse events included constipation (0.7%), diarrhea (0.4%) and dizziness (0.4%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Denke et al[21] Ezetimibe 10 mg QD addition to an ongoing statin therapy vs placebo in addition to an ongoing statin therapy	DB, MC, PC, PG, RCT Men and women ≥18 years of age with diabetes, metabolic syndrome without diabetes, or neither disorder who had LDL levels exceeding the NCEP ATP III goals who were taking a stable, approved dose of any statin, had been following a cholesterol –lowering diet for at least 6 weeks prior to study entry with TG levels ≤350 mg/dL	N=3,030 6 weeks	Primary: LDL reduction and additional lipid parameters, safety and tolerability Secondary: Not reported	Primary: After 6 weeks of treatment, the addition of ezetimibe to ongoing statin therapy reduced LDL levels in patients with diabetes by 28%, metabolic syndrome by 24%, or elevated LDL levels without diabetes or the metabolic syndrome by 26%, compared with a 3% reduction in the placebo group (*P*<0.001 for all). TG and HDL levels were significantly reduced in patients with diabetes and metabolic syndrome when ezetimibe was added to statin therapy compared to placebo (*P*<0.002). Non-HDL levels, TC, apo B:apo AI ratio, and CRP levels improved significantly in patients with diabetes and patients with elevated LDL levels without diabetes or metabolic syndrome when ezetimibe was added to statin therapy compared to placebo. Drug-related adverse events occurred in 5.2% in the placebo group and 5.1% in the ezetimibe group. Drug-related adverse events that led to drug discontinuation occurred in 1.6% in the placebo group and 0.9% in the ezetimibe group. There were no significant differences between the two groups in elevation of ALT, AST or in muscle CK beyond predefined limits. Secondary: Not reported
Pearson, Denke et al[22] Ezetimibe 10 mg QD vs placebo Patients in both groups continued to receive their current	MC, DB, PC, PG Hypercholesterolemic patients ≥18 years of age with LDL-C levels exceeding NCEP ATP III goals while taking a stable, approved dose of any statin, following a cholesterol-lowering diet for at least 6 weeks	N=3,030 6 weeks	Primary: Percent reduction in LDL-C level from baseline after 6 weeks of double-blind treatment Secondary: Percentage of patients who achieved NCEP ATP III target LDL-C levels in	Primary: Ezetimibe added to a statin significantly reduced mean LDL-C levels by an additional 25.8% compared with a reduction of 2.7% with the addition of placebo to statin (95% CI, –24.4% to –21.7%; *P*<0.001). Secondary: The addition of ezetimibe to statin resulted in an additional 23.8% to 25.7% reduction in LDL-C in all NCEP ATP III risk categories. Treatment differences were –24.0%, –19.7%, and –19.9% in the CHD or CHD risk equivalent, multiple risk factors, or <2 risk factors groups, respectively (*P*<0.001 ezetimibe vs placebo for each risk category). No significant differences were found according to age, sex, or race category (*P*>0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dose of statin therapy.			the total population and by NCEP ATP III risk categories (<100 mg/dL for patients with CHD or CHD risk equivalent, <130 mg/dL for patients with multiple CHD risk factors conferring a 10-year risk of CHD of ≤20%, and <160 mg/dL for patients with <2 CHD risk factors)	
Pearson, Denke et al[23] Ezetimibe 10 mg QD in addition to ongoing statin therapy vs placebo in addition to ongoing statin therapy	DB, MC, PG, PC, RCT Men and women ≥18 years of age including white, African American, Hispanic or other who followed a cholesterol-lowering diet, were taking a stable approved dose of any US-marketed statin for at least 6 weeks before study entry, with LDL levels greater than the NCEP ATP III goal	N=3,030 6 weeks	Primary: LDL-C and additional parameters and percentage of patients reaching LDL goal for the NCEP ATP III in racial and ethnic subgroups Secondary: Safety and tolerability	Primary: The addition of ezetimibe to ongoing statin therapy significantly reduced LDL, TC, non-HDL and HDL levels compared to placebo (*P*<0.001). This effect was consistent across race and ethnicity (*P*>0.50 for treatment-by-race interactions). CRP level reduction was statistically significant in patients receiving ezetimibe compared to placebo (*P*<0.001). The treatment-by-race interaction was not statistically significant (*P*=0.83), indicating a consistent treatment effect of lowering CRP levels across race and ethnicity groups. Ezetimibe added to statin therapy significantly increased the percentage of patients attaining their LDL-C goal for the NCEP ATP III in African Americans by 63%, Hispanics by 64.8% and whites by 72.3%, compared to placebo (*P*<0.001). Secondary: The addition of ezetimibe to ongoing statin therapy was well tolerated with an overall safety profile similar in all patient groups by race or ethnicity.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Simons et al[24] Ezetimibe 10 mg QD in addition to an ongoing statin therapy vs placebo in addition to an ongoing statin therapy	OL, phase 4, single arm Men and women from Australia, mean age 65.6 years, with CHD or diabetes mellitus who had already used ≥40 mg/day of a statin for at least 3 months with current TC of >4 mmol/L for existing CHD or >6.5 mmol/L for diabetes or >5.5 mmol/L for diabetes if HDL is <1.0 mmol/L	N=130 6 weeks	Primary: LDL reduction and percentage of patients who reached LDL goal of <2.5 mmol/L or <2.0 mmol/L and other lipid parameters Secondary: Not reported	Primary: The LDL levels after 6 weeks were reduced by 29% (95% CI, 25 to 34) in patients receiving ezetimibe. Goal LDL-C of <2.5 mmol/L and <2.0 mmol/L were reached in 70% and 50% of patients receiving ezetimibe (95% CI, 59% to 79% and 39% to 60%, respectively). TC and TG levels were reduced by 19% and 11%, respectively, in the ezetimibe group compared to placebo (95% CI, –21 to –16 and –16 to –5). There were no significant changes in HDL between the two groups (95% CI, 0 to 6). Secondary: Not reported
Mikhailidis et al[25] Ezetimibe 10 mg QD in combination with a statin vs placebo in combination with a statin or statin monotherapy	MA, systematic review of 19 RCTs, 2 extension studies DB, PG or XO, SB or OL RCTs Adults ≥18 years with diagnoses of nonfamilial or familial hypercholesterolemia, hyperlipidemia, and homozygous familial sitosterolemia; with LDL-C levels above NCEP ATP II/III guideline criteria	N=5,039 Trial durations ranged from 6 to 48 weeks	Primary: Total number of patients attaining LDL-C goal; changes in TC, LDL-C, and HDL-C from baseline to end point Secondary: Not reported	Primary: The analysis of 5 RCTs indicated that when compared to placebo in combination with a statin, the RR of obtaining the LDL-C treatment goal was higher for patients in the ezetimibe and statin groups; *P*< 0.0001. A weighted mean difference (WMD) between treatments significantly favored the ezetimibe and statin combination therapy over placebo and statin: for TC, a WMD of –16.1% (CI, –17.3 to –14.8); for LDL-C, a WMD of –23.6% (CI, –25.6 to –21.7); and for HDL-C, a WMD of 1.7% (CI, 0.9 to 2.5); *P*<0.0001 for all. In an analysis of patients with or without CHD (in addition to hypercholesterolemia), the ezetimibe and statin combination was favored over placebo and statin for the following WMD: LDL-C –23.6% (*P*<0.0001); TC –16.1% (*P*<0.0001); HDL-C +1.7% (*P*<0.0001); TG –10.7%; Apo B –17.3%; RR, LDL-C treatment goal 3.4 (*P*<0.0001). The difference between treatments in all studies favored the ezetimibe and statin combination therapy for all outcomes except TG and HDL-C. An analysis of data from a 48-week extension study correlated with the pooled estimates of the short-

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				term studies in the meta-analysis. This data showed that the ezetimibe and simvastatin combination resulted in significantly lower levels of LDL-C, TC, and TG when compared with the placebo and simvastatin combination (reductions of 20.4%, 13.4% and 13.6%, respectively; P<0.001 for the difference between treatments). Secondary: Not reported
Ballantyne, Houri et al[26] Ezetimibe 10 mg QD vs atorvastatin 10, 20, 40, or 80 mg QD vs ezetimibe 10 mg QD plus atorvastatin 10, 20, 40, or 80 mg QD vs placebo	DB, PC, RCT Men and women aged ≥18 years with primary hypercholesterolemia (LDL-C 145-250 mg/dL and TG ≤350 mg/dL)	N=628 12 weeks	Primary: Percentage reduction in direct LDL-C from baseline to final assessment Secondary: Change from baseline to final assessment for calculated LDL-C, TC, TG, HDL-C, TC:HDL-C ratio, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, Lp(a), direct LDL-C:HDL-C ratio, adverse events	Primary: There was a significantly greater mean reduction of direct LDL-C from baseline to final assessment in the ezetimibe plus atorvastatin group compared to either atorvastatin alone (P<0.01) or ezetimibe alone (P<0.01). Mean changes in direct LDL-C ranged from –50% to –60% in the combination group compared to –35% to –51% in the atorvastatin alone group (P<0.01). Secondary: Calculated LDL-C was also significantly reduced more commonly in the combination group than all doses of atorvastatin monotherapy (P<0.01). Greater reductions in LDL-C, TC, and TG were observed with increasing doses of atorvastatin monotherapy. However, there was not a favorable dose response with HDL-C. There were similar reductions in LDL-C (50% vs 51%), TC:HDL-C ratio (43% vs 41%), and TG (both 31%) with coadministration of ezetimibe plus atorvastatin 10 mg and the maximal dose of atorvastatin monotherapy, respectively. However, there was a significantly greater increase in HDL-C (9% vs 3%) with the combination group (P value not reported). Reductions in apo B, non–HDL-C, and direct LDL-C:HDL-C ratio from baseline were significantly greater in the combination group compared to both atorvastatin monotherapy (P<0.01 for all) and ezetimibe monotherapy (P<0.01 for all). However, increases in HDL_2-C (P=0.53), HDL_3-C (P=0.06), apo AI (P=0.31), and Lp(a) (P=0.50) did not significantly differ between the combination therapy

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and atorvastatin monotherapy groups. There also was no significant difference between the combination therapy and ezetimibe monotherapy groups for increases in these same parameters: HDL_2-C (*P*=0.08), HDL_3-C (*P*=0.67), apo AI (*P*=0.80), and Lp(a) (*P*=0.92). The combination of ezetimibe plus atorvastatin was well-tolerated. Treatment-emergent adverse events were reported in 17% of patients receiving atorvastatin monotherapy and 23% of patients receiving combination therapy. The majority of adverse events were mild to moderate in severity (*P* value not reported).
Kerzner et al[27] Ezetimibe 10 mg QD vs lovastatin 10, 20, or 40 mg QD vs ezetimibe 10 mg QD plus lovastatin 10, 20, or 40 mg QD vs placebo	DB, MC, PC, RCT Men and women aged ≥18 years with mean plasma LDL-C 145 to 250 mg/dL as calculated by Friedewald equation, mean TG ≤350 mg/dL	N=548 12 weeks	Primary: Percentage decrease in directly measured LDL-C from baseline to study end point Secondary: Change from baseline to end point for calculated LDL-C, TC, TG, HDL-C, apo B, non–HDL-C, HDL_2-C, HDL_3-C, apo AI, direct LDL-C:HDL-C ratio, adverse events	Primary: The reduction in plasma levels of direct LDL-C from baseline to end point was significantly greater in the combination group of ezetimibe plus lovastatin compared to either lovastatin or ezetimibe monotherapy (*P*<0.01 for both). The mean percentage decrease in direct LDL-C in the combination group was significantly greater than the decrease obtained from the corresponding lovastatin dose or next higher dose of lovastatin monotherapy (*P*<0.01). The mean percentage change in LDL-C achieved with combination ezetimibe plus lovastatin 10 mg was similar to the highest lovastatin dose of 40 mg monotherapy (*P*=0.10). Secondary: In comparison to lovastatin monotherapy, the combination group significantly improved calculated LDL-C, TC, TG, HDL-C, apo B, non–HDL-C, HDL_2-C, HDL_3-C, direct LDL-C:HDL-C ratio (*P*<0.01 for all), and apo AI (*P*=0.04). The combination of ezetimibe plus lovastatin significantly increased HDL-C at lovastatin doses of 20 and 40 mg compared to the same lovastatin monotherapy dose (*P*<0.01 and *P*<0.02, respectively) and significantly decreased TG levels (*P*<0.01 for both). Treatment-related adverse events were reported for 16% of patients receiving lovastatin monotherapy and 17% of patients receiving combination therapy. The safety profile for the combination group was similar to that for the lovastatin

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				monotherapy and placebo group (*P* value not reported).
Melani et al[28] Ezetimibe 10 mg QD vs pravastatin 10, 20, or 40 mg QD vs ezetimibe 10 mg QD plus pravastatin 10, 20, or 40 mg QD vs placebo	DB, MC, PC, RCT Men and women 20-86 years old with primary hypercholesterolemia (LDL-C 3.8 to 6.5 mmol/L as calculated by the Friedewald equation and TG ≤4.0 mmol/L)	N=538 12 weeks	Primary: Percent change in direct LDL-C from baseline to study end point Secondary: Mean change and percent change from baseline in LDL-C as calculated by the Friedewald equation, TC, TG, HDL-C, direct LDL-C:HDL-C and TC:HDL-C ratio, non–HDL-C, apo AI, apo B, HDL_2-C, HDL_3-C, Lp(a)	Primary: A mean percent change of –38% for the combination therapy and –24% for pravastatin monotherapy was observed. The combination therapy was significantly more effective at reducing plasma levels of direct LDL-C from baseline to end point (*P*<0.01). The combination group had a mean percentage change in direct LDL-C ranging from –34% to –41% compared with –20% to –29% for individual doses of pravastatin monotherapy. When the combination therapy was compared to its corresponding pravastatin dose, the incremental mean percentage reductions in direct LDL-C were statistically significant in favor of the combination therapy (*P*≤0.01). In addition, the coadministration of ezetimibe plus pravastatin 10 mg produced a larger mean percentage reduction in direct LDL-C compared to the highest dose of pravastatin monotherapy (*P*≤0.05). Secondary: In comparison to pravastatin monotherapy, the combination therapy improved calculated LDL-C, TG, TC, apo B, non–HDL-C, direct LDL-C:HDL-C, and TC:HDL-C (*P*<0.01 for all). Both direct and calculated LDL-C levels at all pravastatin doses were significantly reduced in the combination group (*P*<0.01). TG was also significantly reduced in the combination group at pravastatin doses of 10 and 20 mg compared to pravastatin monotherapy (*P*<0.05). Although the combination therapy produced greater increases in HDL-C at the 10 and 40 mg doses, it was not significant. The differences in change in HDL_2-C, HDL_3-C, apo AI, and Lp(a) between the combination group and pravastatin monotherapy were determined to be not significant (*P*=NS). Coadministration of ezetimibe and pravastatin was well tolerated and the overall safety profile was similar to pravastatin monotherapy and placebo. There was no evidence to suggest that combination therapy would increase the risk of developing any nonlaboratory adverse event (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Farnier et al[29] Ezetimibe 10mg vs micronized fenofibrate 160 mg vs ezetimibe 10 mg in combination with micronized fenofibrate 160 mg vs placebo	DB, MC, PC, RCT Men and women 18 to 75 years of age with mixed hyperlipidemia and no CHD, CHD-equivalent disease (except for type 2 diabetes), or 10-year CHD risk >20%	N=619 12 weeks	Primary: Percent change in LDL-C from baseline to study end point Secondary: Percent change in other lipid, non-lipid, and lipoprotein parameters from baseline to study end point	Primary: The mean percent change in LDL-C reduction was significantly greater in the micronized fenofibrate and ezetimibe group when compared with the other treatment groups (*P*<0.001 compared with micronized fenofibrate and ezetimibe). These reductions were –13.4% in the ezetimibe group, –5.5% in the micronized fenofibrate group, and –20.4% in the micronized fenofibrate and ezetimibe group. Secondary: When compared with micronized fenofibrate or ezetimibe monotherapy, significant reductions in apo B, non–HDL-C and LDL-C were observed in the micronized fenofibrate and ezetimibe group; *P*<0.001. When compared with placebo, significant decreases in TG levels and significant increases in HDL-C level were observed in both the micronized fenofibrate plus ezetimibe and micronized fenofibrate treatment groups; *P*<0.001. The percent changes from baseline to study end point were as follows: –11.8% in TC, 3.9% in HDL-C, –11.1% in TG, and –6.1% in high sensitivity CRP in the ezetimibe group; –10.8% in TC, 18.8% in HDL-C, –43.2% in TG, and –28.0% in hsCRP in the micronized fenofibrate group; –22.4% in TC, 19.0% in HDL-C, –44.0% in TG, and –27.3% in high sensitivity CRP in the micronized fenofibrate and ezetimibe group; *P*<0.05 for all.
McKenney et al[30] Ezetimibe 10 mg QD and fenofibrate 160 mg (single entities) vs fenofibrate 160 mg	DB, ES, RCT Extension of the preceding study by Farnier et al Patients with mixed hyperlipidemia, LDL-C 130 to 220 mg/dL, TG 200 to 500 mg/dL	N=576 48 weeks	Primary: Percent change in LDL-C from baseline Secondary: Percent change in TC, HDL-C, TG, non–HDL-C, apo B, apo AI, and hsCRP from baseline	Primary: The combination resulted in significantly reduced LDL-C compared with monotherapy (–22.0 vs –8.6; *P*<0.001). Secondary: The combination resulted in significantly reduced TC, TG, non–HDL-C, and apo B compared with monotherapy (–23.2 vs –13.6; *P*<0.001), (–46.0 vs –41.8; *P*=0.002), (–31.6 vs –19.4; *P*<0.001), (–25.2 vs –16.2; *P*<0.001). The combination resulted in significantly increased HDL-C compared with monotherapy (20.9 vs 17.8; *P*=0.02). There were no significant differences in apo AI or hsCRP (*P*=not significant).
Coll et al[31]	RCT	N=20	Primary: LDL-C, TC,	Primary: Ezetimibe-treated patients experienced a 20% (*P*=0.002) LDL-C reduction and a

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ezetimibe 10 mg QD vs fluvastatin extended release 80 mg QD	HIV patients, ≥6 months on stable HAART, ≥18 years of age, fasting LDL ≥3.30 mmol/L	6 weeks	endothelial function Secondary: Not reported	10% TC reduction (*P*=0.003). Fluvastatin-treated patients experienced a 24% LDL-C reduction (*P*=0.02) and a 17% TC reduction (*P*=0.06). There were no significant differences in lipid-lowering ability between groups. Ezetimibe-treated patients did not experience significant changes in endothelial function. Fluvastatin-treated patients experienced an increase in the rate of endothelial function by 11% (*P*=0.5). Secondary: Not reported
Blagden et al[32] Ezetimibe 10 mg QD and atorvastatin 10 mg QD vs placebo and atorvastatin 10 mg QD	DB, MC, PC, RCT Men and women with primary hyper-cholesterolemia and CHD	N=148 6 weeks	Primary: Mean percentage change in LDL-C from baseline to study end point Secondary: Percentage of patients achieving the new Joint British Society 2 (JBS 2) recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L, percentage of patients reaching LDL-C targets, safety and	Primary: From baseline to week 6, ezetimibe and atorvastatin provided significantly greater reductions in adjusted mean LDL-C level compared with atorvastatin monotherapy, (–50.5% vs –36.5%; *P*<0.0001), equating to an additional 14.1% reduction (95% CI, –17.90 to –10.19). Secondary: A significantly higher proportion of patients on ezetimibe and atorvastatin achieved the new JBS 2 recommended LDL-C goal of <2 mmol/L and the JBS 2 minimum treatment standard of <3 mmol/L compared with atorvastatin monotherapy (62% vs 12%; *P*<0.0001 and 93% vs 79%, respectively). Patients receiving ezetimibe and atorvastatin were 12 times more likely to reach LDL-C targets (OR, 12.1; 95% CI, 5.8 to 25.1; *P*<0.0001) compared with patients receiving atorvastatin monotherapy. Clinical chemistry profiles and the incidence of adverse events were similar in both groups (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			tolerability	
Stein et al[33] Ezetimibe 10 mg QD in combination with atorvastatin 10 mg QD (titrated up to 40 mg/day) vs atorvastatin 20 mg QD (titrated up to 80 mg/day)	DB, DD, MC Men and women ≥18 years of age with primary hypercholesterolemia and documented CHD, at least 2 cardiovascular risk factors, or heterozygous familial hypercholesterolemia with an LDL-C level ≥130 mg/dL despite treatment with 10 mg QD of atorvastatin and diet	N=621 14 weeks	Primary: Percentage of subjects in the 2 treatment groups achieving an LDL-C level ≤100 mg/dL after 14 weeks randomization Secondary: Effects on other lipid parameters 4 weeks after randomization	Primary: When compared to atorvastatin monotherapy, a significantly higher percentage of subjects in the ezetimibe and atorvastatin reached an LDL-C level ≤100 mg/dL after 14 weeks randomization, respectively 7% vs 22%; *P*<0.01. Secondary: When compared to atorvastatin monotherapy, significant reductions in LDL-C, TC and TG levels were observed in subjects in the ezetimibe and atorvastatin; *P*<0.01. Respectively, percent changes between combination vs atorvastatin monotherapy were –22.8 vs –8.6% (mean change) in LDL-C levels, –17.3% vs –6.1% in TC levels (mean change), and –9.3% vs –3.9% (median change) in TG levels; *P*<0.01 for all. Nonsignificant changes were observed in HDL-C levels; *P* value not reported.
Ballantyne, Weiss et al[34] Ezetimibe 10 mg QD and rosuvastatin 40 mg QD vs rosuvastatin 40 mg QD	MC, OL, PG, RCT Men and women aged ≥18 years with hypercholesterolemia, history of CHD or clinical evidence of atherosclerosis or CHD risk equivalent (10-year CHD risk score >20%), 2 most recent fasting LDL-C levels of ≥160 mg/dL and <250 mg/dL	N=469 6 weeks	Primary: Percentage of patients achieving the NCEP ATP III LDL-C goal (<100 mg/dL) after 6 weeks of treatment Secondary: Percentage of patients achieving the ATP III non–HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200	Primary: Significantly more patients in the combination therapy group achieved the LDL-C goal of <100 mg/dL at week 6 compared to rosuvastatin alone (94% vs 79.1%; *P*<0.001). Secondary: The non–HDL-C goal of <130 mg/dL and LDL level <100 mg/dL when baseline TG ≥200 mg/dL were achieved by a significantly higher percentage of patients in the combination therapy group than the monotherapy group (88 patients or 37.4% and 80 patients or 34.8%, respectively; *P*<0.001). There was a significantly higher percent of patients in the combination therapy group achieving the European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals (LDL <100 or 115 mg/dL and TC <175 or 190 mg/dL), depending on risk category compared to the rosuvastatin group alone at week 6 (LDL 93.6% vs 74.3%, LDL and TC 90.6% vs 68.3%, respectively; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			mg/dL, percentage of patients achieving the 2003 European LDL goal of <100 or 115 mg/dL and combined LDL and TC goals of <100 or 115 mg/dL and <175 or 190 mg/dL, respectively, depending on risk category, percentage change from baseline in LDL, HDL, TC, TG, non-HDL, lipid ratios (LDL:HDL, TC:HDL and non-HDL:HDL), apo AI, apo B, and apo B:apo AI ratio, and changes in hsCRP in at week 6, safety and tolerability	At week 6, the combination therapy group had a significantly greater percent reduction of 69.8% in the LDL level compared to a 57.1% reduction in the monotherapy group (*P*<0.001). Significantly greater reductions in TC, non–HDL-C and TG levels were seen in the combination group compared to the monotherapy group (*P*<0.001). Both treatment groups increased HDL level to a similar extent (*P*=0.151). LDL:HDL, TC:HDL and non-HDL:HDL cholesterol ratios decreased significantly more in patients receiving combination therapy compared to patients receiving monotherapy (all *P*<0.001). Significant decreases in apo B and the apo B:apo AI ratio were seen in the combination therapy group compared to the monotherapy group (*P*<0.001 for both). Apo AI increased by 3.2% and 1.6% in the combination therapy and monotherapy groups, respectively (*P*=0.202). The median percent decrease in CRP was significantly higher with combination therapy than monotherapy (–46.4% vs –28.6%; *P*<0.001). The overall frequency and type of adverse events were similar in both groups, with 31.5% of patients on combination therapy and 33.5% of patients on monotherapy reporting any adverse event (*P* value not provided). No adverse events were considered related to ezetimibe; the most frequently reported adverse event was myalgia (3.0% of patients in the rosuvastatin-alone group and 2.9% in the rosuvastatin plus ezetimibe group). There were 2 patients (0.8%) in the combination therapy group and 3 patients (1.3%) in the monotherapy group who discontinued the study due to treatment-related adverse events. One death occurred in the combination therapy group due to acute myocardial infarction and this was not considered to be related to study treatment. ALT increases >3 times the upper limit of normal were recorded in 3 patients, all in the combination therapy group.
Patel et al[35] Ezetimibe 10 mg QD and simvastatin 20 mg QD vs	DB, MC, PC, PG, RCT Men and women aged 18-75 years with primary hyper-cholesterolemia (LDL ≥3.3 mmol/L and ≤4.9	N=153 6 weeks	Primary: Mean change in LDL cholesterol level from baseline to 6 weeks and the proportion of patients who	Primary: At 6 weeks, patients receiving ezetimibe and simvastatin combination therapy had a mean LDL reduction of 14.6% (95% CI, 10.1 to 19.1). At 6 weeks, a greater number of patients receiving ezetimibe and simvastatin combination therapy reached an LDL goal <3 mmol/L compared to patients receiving monotherapy (93% vs 75%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
simvastatin 20 mg QD	mmol/L, TG <3.99 mmol/L) and documented CHD at least 3 months prior to baseline who were not receiving pharmacologic lipid management therapy		reached an LDL goal of <3 mmol/L at end point Secondary: Changes in serum TC, TG and HDL levels, and safety and tolerability	Secondary: At 6 weeks, there was a significant additional reduction in TC of 0.69 mmol/L in patients receiving ezetimibe and simvastatin combination therapy compared to patients receiving ezetimibe monotherapy (95% CI, 0.48 to 0.90; *P*<0.0001). There was a 20.4% reduction in TG levels in the combination group compared to a 12.4% reduction in the monotherapy group (*P*=0.06). Baseline HDL levels increased by 6% in both treatment groups (*P* value not provided). In the combination group, 40% of patients had at least one treatment-emergent adverse event compared to 25% in the monotherapy group. The overall incidence of adverse events were not significant among the two groups (*P*=0.07). Two patients in the combination therapy group and 1 patient in the monotherapy group experienced a serious adverse event unrelated to the study medications.
Landry et al[36] Ezetimibe 10 mg QD and simvastatin 20 mg QD (single entities) vs placebo and simvastatin 20 mg QD (single entities)	MC, RCT Men and women ≥18 years of age, patients on predialysis with creatinine level ≥1.7 mg/dL, hemodialysis, or peritoneal dialysis	N=203 6 months	Primary: LDL-C, TC, non–HDL-C, HDL-C, TG, apo B, apo AI Secondary: Tolerability and safety	Primary: Both groups had statistically reduced LDL-C at 1, 3, and 6 months compared to baseline (*P*<0.0001). The addition of ezetimibe to simvastatin was associated with 27%, 26%, and 21% reductions in LDL-C at 1, 3, and 6 months, respectively. The addition of ezetimibe to simvastatin was associated with 16%, 16%, and 14% reductions in TC at 1, 3, and 6 months, respectively. The addition of ezetimibe to simvastatin was associated with 24%, 25%, and 19% reductions in non–HDL-C at 1, 3, and 6 months, respectively. The addition of ezetimibe to simvastatin was associated with 15%, 14%, and 12% reductions in apo B at 1, 3, and 6 months, respectively. There were no significant effects in HDL-C, TG, or apo AI (*P*=not significant) except for 7% increase of HDL-C at 3 months (*P*=0.02). Secondary: There were no significant differences in muscle pain, muscle weakness, abdominal discomfort, nausea, constipation, or appetite loss between groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(*P*=NS). More patients on ezetimibe reported diarrhea (27% vs 12%; *P*=0.009). There were no significant differences in CK levels or abnormal hepatic transaminase levels (*P* value not reported).
Kastelein et al[37] ENHANCE Simvastatin 80 mg daily and placebo vs simvastatin 80 mg daily and ezetimibe 10 mg daily	DB, MC, PRO, RCT Men and women between the ages of 30 and 75 years with FH regardless of their previous treatment with lipid-lowering drugs, baseline LDL-C at least 210 mg/dL without treatment; patients were excluded if they had high-grade stenosis or occlusion of the carotid artery, history of carotid endarterectomy or carotid stenting, homozygous FH, NYHA class III or IV congestive heart failure, cardiac arrhythmia, angina pectoris or recent cardiovascular events	N=720 24 months (plus 6-week run-in period with placebo)	Primary Change in mean carotid artery IMT (defined as average of means of far wall IMT of right and left common carotid arteries and bulbs and internal carotid arteries) Secondary: Proportion of patients with regression in the mean carotid artery IMT or new carotid artery plaques of more than 1.3 mm, change from baseline in mean maximal carotid artery IMT and average mean IMT of carotid and common femoral arteries, lipid	Primary The mean change in the carotid artery IMT was 0.0058±0.0037 mm in the simvastatin monotherapy group and 0.0111±0.0038 mm in the simvastatin-ezetimibe group (*P*=0.29). Secondary: There was no significant difference in the proportion of patients with regression in the mean carotid artery IMT (44.4% vs 45.3%; *P*=0.92) or new plaque formation (2.8% vs 4.7%; *P*=0.20) receiving simvastatin vs simvastatin-ezetimibe, respectively. No significant change from baseline was reported in the mean maximum carotid artery IMT (0.0103±0.0049 mm and 0.0175±0.0049 mm, respectively; *P*=0.27). No significant changes were observed between study groups regarding mean measures of IMT of the common carotid artery (*P*=0.93), carotid bulb (*P*=0.37), internal carotid artery (*P*=0.21) and femoral artery (*P*=0.16) or average of the mean values for carotid and femoral artery IMT (*P*=0.15). After 24 months, mean LDL-C decreased by 39.1 mg/dL in the simvastatin group and by 55.6 mg/dL in the combination group (between-group difference of 16.5%; *P*<0.01). Reductions in TG (between-group difference of 6.6%; *P*<0.01) and CRP (between-group difference of 25.7%; *P*<0.01) were significantly higher with simvastatin-ezetimibe than simvastatin alone. Adverse events (29.5% vs 34.2%; *P*=0.18) and discontinuation rates (9.4% vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			parameters, CRP, adverse events	8.1%; *P*=0.56) were similar between simvastatin monotherapy and the combination therapy.
Bays et al[38] Ezetimibe 10 mg QD and colesevelam 3.8 g QD vs placebo and colesevelam 3.8 g QD	DB, MC, PC, PG, RCT Men and women with primary hyper-cholesterolemia	N=86 4-8 weeks washout period and 6 weeks of treatment	Primary: Mean percent change in LDL-C, mean absolute and mean percent change in HDL-C, non–HDL-C, TC, apo AI and apo B, and median absolute and percent changes in TG and hsCRP from baseline to end of treatment Secondary: Safety and tolerability	Primary: After 6 weeks of treatment, ezetimibe plus colesevelam produced a mean percent decrease in LDL-C of 32.3% vs 21.4% with ezetimibe monotherapy; *P*<0.0001. Ezetimibe plus colesevelam was significantly more effective than ezetimibe alone at producing mean percent reductions in TC, non–HDL-C, apo B and increases in apo AI (*P*<0.005 for all). Neither treatment regimen resulted in significant changes in median TG levels compared with baseline (*P*=NS). Secondary: Both treatment groups were safe and generally well tolerated.
Jelesoff et al[39] Ezetimibe 10 mg daily and niacin (single entities) vs niacin	RETRO Patients who received ezetimibe as add-on therapy to stable doses of niacin and other lipid medications	N=53 Not reported	Primary: TC, LDL-C, TG, HDL-C Secondary: Percent change in patients meeting NCEP ATP III treatment guidelines	Primary: The addition of ezetimibe resulted in reductions of 18%, 25%, and 17% (*P*<0.001) for TC, LDL-C, and TG, respectively. There were no significant differences in HDL-C (*P*=NS). Secondary: 13% of patients met goals prior to addition of ezetimibe while 45% of patients met goals following addition of ezetimibe (*P*<0.001).

Drug regimen abbreviations: QD=daily
Study abbreviations: CI=confidence interval, DB=double=blind, ES=extension study, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized control trial, RETRO=retrospective, RR=relative risk, SB=single blind, SD=standard deviation, WMD=weighted mean difference, XO=cross over
Miscellaneous abbreviations: apo AI=apolipoprotein AI, apo B=apolipoprotein B, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BMI=body mass index, CAD=coronary artery disease, CHD=coronary heart disease, CK=creatine kinase, CRP=C-reactive protein, FH=familial hypercholesterolemia, HAART=highly active antiretroviral therapy, HDL=high-density lipoprotein, HDL-C=high-

density lipoprotein cholesterol, HDL_2=HDL subfraction 2, HDL_3=HDL subfraction 3, HIV=human immunodeficiency virus, hsCRP=high-sensitivity C-reactive protein, IMT=intima-media thickness, JBS=Joint British Society, LDL-C=low-density lipoprotein cholesterol, LDL-C:HDL-C=low-density lipoprotein cholesterol:high-density lipoprotein cholesterol ratio, Lp(a)=lipoprotein(a), NCEP ATP=National Cholesterol Education Program Adult Treatment Panel, non–HDL-C=non-high-density lipoprotein cholesterol, NYHA=New York Heart Association, TC=total cholesterol, TC:HDL-C=total cholesterol:high-density lipoprotein cholesterol ratio, TG=triglyceride, VLDL=very low-density lipoprotein

IX. Conclusions

There are no generic products in this class. At this time, ezetimibe is the only cholesterol absorption inhibitor and appears to be a safe and modestly effective agent for the reduction of low-density lipoprotein cholesterol (LDL-C). Additional data is necessary to determine its effects on high-density lipoprotein cholesterol (HDL-C) and triglycerides.

HMG-CoA reductase inhibitors (statins) are considered first-line agents for treating hyperlipidemia due to their ability to lower total cholesterol and LDL-C. As monotherapy, ezetimibe provides only modest reductions in LDL-C. Ezetimibe's primary role is in combination with a statin in patients unable to achieve or sustain target low-density lipoprotein levels on a statin alone or to reduce the dose of a statin required to achieve target levels. The unique mechanism of action of ezetimibe allows for an additional reduction in LDL-C when administered with a statin. Although studies have shown that the combination of ezetimibe and a statin is more efficacious in lowering LDL-C than monotherapy with either agent, the recently published results of the ENHANCE trial (Effect of Combination Ezetimibe and High-Dose Simvastatin vs Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia) did not show that these reductions led to better clinical outcomes.[37]

The ENHANCE trial consisted of 720 patients with heterozygous familial hypercholesterolemia and the primary end point was the mean change in the intima-media thickness measured at three sites in the carotid artery.[37] No significant difference was found in this primary end point between simvastatin-ezetimibe 80/10 mg compared to simvastatin 80 mg alone during the two-year study period. Combination therapy with ezetimibe and simvastatin significantly lowered LDL-C by 16.5% compared to simvastatin alone.

X. Recommendations

In recognition of ezetimibe's primary role in combination with a statin in patients unable to achieve or sustain target LDL levels on a statin alone, its modest LDL-lowering capacity, and the lack of available robust long-term safety, efficacy, and outcomes data, no changes are recommended to the current approval criteria.

Zetia® requires prior authorization with the following approval criteria:

- The patient has a documented side effect, allergy or contraindication (eg. drug interaction) to a statin.

<u>OR</u>

- The patient has a diagnosis of homozygous sitosterolemia.

<u>OR</u>

- The patient has had an inadequate response to BOTH generic simvastatin and Crestor®

<u>AND</u>

- The quantity requested does not exceed 1 tablet per day.

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